NTP
National Toxicology Program

Diethyl Phthalate Concept Review

Project leader: Dr. Paul Foster

NTP Board of Scientific Counselors
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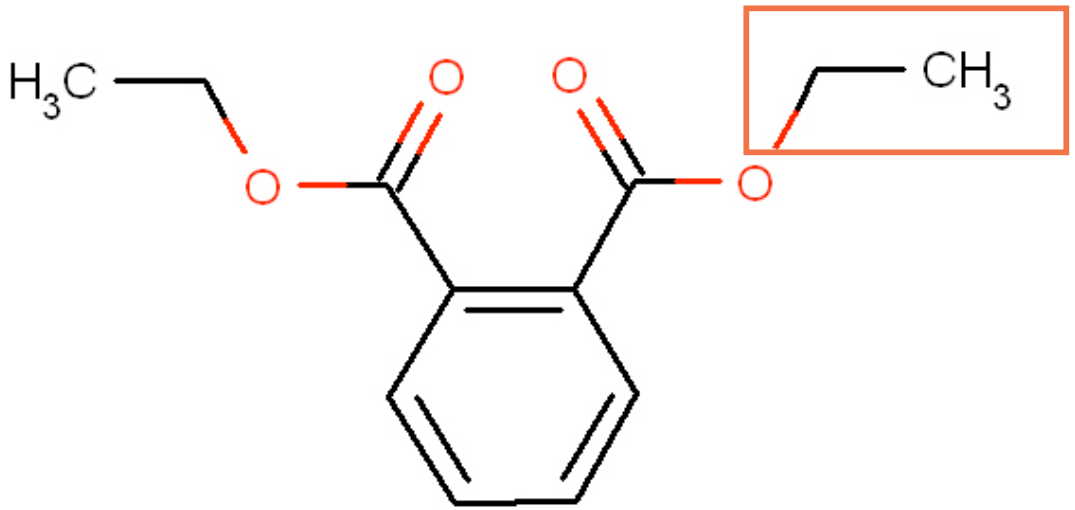
Background and Nomination

- **Nomination.**
  - Diethyl Phthalate (DEP) was nominated by NIEHS.
- **Uses**
  - As a solvent, including in personal care products and fragrances.



Background

- Concerns regarding phthalate esters
  - As a class phthalates show an age susceptibility in response for reproductive toxicity.
    - fetal> neonatal>pubertal>adult
  - Greatest concern is the induction of effects *in utero* on reproductive development.
    - Antiandrogen action – some effects that may not be manifest until later in life (e.g DBP, DEHP).
    - Resemble the human Testicular Dysgenesis Syndrome.
  - Species differences in susceptibility to the reproductive and antiandrogenic effects
    - rat >> mouse.

Multigeneration/ transgenerational studies in animals

- The NTP conducted an RACB study in the mouse (an insensitive model for phthalates) with DEP at dose levels up to 2.5% in the diet.
  - Overall conclusions - no biologically significant effects.
  - F_1 generation data revealed small changes not seen in the parental generation.
- Recent dietary study in the rat did not report any treatment related reproductive effects.
  - Did not include some specific antiandrogenic end points sensitive to phthalates (e.g nipple retention).
- Significant questions regarding the experimental power of standard multigeneration studies to detect developmental changes in adults.
  - Only 1 male and female selected from each litter raised to adulthood. A conventional prenatal developmental toxicity study examines every pup in a litter.
- No effects in fetuses or offspring after DEP administration to pregnant rats on antiandrogenic effects, or gene expression changes characteristic of DBP or DEHP.
  - Studies were small, single dose level, designed to examine SAR.

Human Data

- **Exposure**
  - Number of the NHANES studies reported by the CDC
    - DEP metabolite concentrations highest of any individual phthalate in urine from the general population.
    - DEP metabolites in most urine samples analyzed.
  - DEP metabolites in amniotic fluid taken from women in the general population (small study of 54 samples).
- **Epidemiology Studies**
  - DEP metabolite concentration in maternal urine positively correlated with decreased anogenital index in male offspring.
  - DEP metabolite concentrations in mothers' breast milk correlated with the LH: free testosterone ratio in their 6-month old male infants.
  - The changes in these end points in humans are consistent with the effects of other phthalates on androgen signaling in rats.
    - No correlation with DEHP metabolites. Correlations may be related to overall phthalate exposure.

HYPOTHESIS

- The null hypothesis is that DEP does not affect reproduction, or reproductive development, in rats and is unlikely to present a risk to humans.

Proposed Research Project

- Conduct a robust dietary multigeneration study in the rat.
- Include phenotypic end points known to be sensitive to the antiandrogenic effects of other phthalates.
- The study should encompass a wide range of dose levels.
- The study design should incorporate an increased number of pups retained to adulthood for examination, rather than removed at weaning.
- A NTP study with this type of design (on DEHP) has shown significantly increased ability to detect reproductive tract effects in the F_1 and F_2 generations at lower dose levels compared to the conventional multigeneration design.
- Undertake toxicokinetic studies on dose delivery to the fetus (including amniotic fluid) and the pup for comparison to DEP human exposure studies.

Significance

- These studies would fill the critical data gaps for DEP for which public health concern has been raised due to:
  - Its higher human exposure compared to other members of the class.
  - Some small, human studies linking maternal exposure to DEP with alterations in androgen levels/ status in the offspring.
- Crucial to estimate whether DEP exposure contributes any additional, cumulative risks for humans that have multiple phthalates in their tissues and fluids.